Amendments to the Specification

Page 1, after the title of the invention insert the following:

This application is a Continuation application of application Serial No. 10/462,726, filed June 17, 2003 which is a Divisional application of application Serial No. 10/340,601, filed January 13, 2003.

Page 1, please replace the paragraphs spanning line 14 through page 3, line 21, with the following rewritten paragraphs:

Zonisamide has widely been used as an antiepileptic agent in Japan and the United ~~Unite~~ States. Zonisamide and processes for the preparation thereof are disclosed in JP-A-53-77057, USP 4,172,896 and JP-A-54-163823. In addition, Yakugaku-Zasshi, vol. 116, p. 533-547 (1996) discloses that zonisamide has actually been prepared using as an intermediate 1,2-benzisoxazole-3-methanesulfonyl chloride, which is obtained by sulfonation and decarboxylation of 1,2-benzisoxazol-3-acetic acid. Further, the solvent for the above sulfonation and decarboxylation is dichloromethane in the process disclosed in Yakugaku-Zasshi, vol. 116, p. 533-547 (1996), and 1,2-dichloroethane in the process disclosed in JP-A-53-77057.

The solvent used in the preparation of a drug substance cannot completely be removed by practical manufacturing techniques, which are in actuality employed in the production. Therefore, in the preparation of drug substance wherein plural steps are serially carried out till the final step, each solvent used in each step may possibly ~~residue in~~ remain in a residual amount in the drug substance. Further, residual solvents ~~to residue~~ in the drug substance usually cannot be useful for the therapeutic benefits of the drug substance, and contrarily, there may be caused a problem of safety of a patient according to the kinds of residual solvents and a concentration thereof. In terms of improving and increasing the safety of drugs, "IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS", ICH Harmonized Tripartite Guideline, 17 July 1997 was made in INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH).

Since a solvent may play an important role in increasing the yield rate or in determination of physical properties of drug substance such as crystal form, purity, solubility, etc., even if such a solvent is known to be toxic, there may be many cases that the use thereof in the preparation of drug substance cannot be avoided in terms of risk-benefits. In such cases, this guideline decrees that a concentration of a residual solvent in the drug substance should be not more than a ~~value of~~ limit which is toxicologically acceptable.

A solvent for the preparation of the intermediate for zonisamide, 1,2-benzisoxazole-3~~2-methansulfonyl~~ methanesulfonyl chloride, is ~~rather~~ 1,2-dichloroethane rather than dichloromethane. ~~Because~~ This is because, during the decarboxylation, which is carried out after the sulfonation of 1,2-benzisoxazole-3-acetic acid, the reaction mixture requires to be heated at about 60°C, which is higher than the boiling point of dichloromethane. In addition, 1,2-dichloroethane can be used as well in the step of preparation of zonisamide by reacting 1,2-benzisoxazole-3-methanesulfonyl chloride with ammonia. However, when zonisamide is prepared using 1,2-dichloroethane, the residual concentration thereof should be not more than 5 ppm as defined in the above-mentioned guideline "IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS". This guideline is not applied to the drugs, which are already on market, but it is very important to prepare a drug substance complying with this guideline in terms of safety of drugs.

Page 4, please replace the paragraph spanning line 12 through page 5, line 1, with the following rewritten paragraph:

The present inventors have intensively studied a process for the preparation of crystals of zonisamide having a high safety and complying with the above-mentioned guideline, and have found that the desired crystals of zonisamide containing residual 1,2-dichloroethane of not more than 5 ppm can easily be obtained even from crystals of zonisamide containing 1,2-dichloroethane in a high concentration, by using an aqueous C_{2-4} alcohol, i.e., by the steps of adding an aqueous C_{2-4} alcohol to said crystals and distilling ~~distillating~~ the resulting mixture, followed by crystallization, without equipping any additional apparatus to existing ones, or without repetition of recrystallization, and

further there are no affects on the yield thereof, and finally the present inventors have accomplished the present invention.

Page 6, please replace the paragraph spanning lines 13-18, with the following rewritten paragraph:

The "aqueous C_{2-4} alcohol" means a mixture of water and a C_{2-4} alcohol, and the "C_{2-4} alcohol" includes, for example, ethanol, propanol, isopropanol, and 2-butanol. The "aqueous C_{2-4} alcohol" is preferably aqueous ethanol, aqueous propanol, ~~and~~ or aqueous isopropanol, among them aqueous isopropanol is most preferable.

Page 7, please replace the paragraph spanning lines 5-11, with the following rewritten paragraph:

The ~~steps from dissolving the starting crystals of zonisamide in an aqueous C_{2-4} alcohol to~~ step of removing 1,2-dichloroethane by azeotropic distillation ~~are~~ is usually carried out subsequently to the step of dissolving the starting crystals of zonisamide in an aqueous C_{2-4} alcohol. The temperature for dissolving the starting crystals of zonisamide is not necessarily specified, but it is usually in the range of from 30°C to a boiling point of the C_{2-4} alcohol to be used.

Page 8, please replace the paragraph spanning lines 3-18, with the following rewritten paragraph:

The distillation may be carried out either under atmospheric pressure or under reduced pressure, but preferably is carried out under atmospheric pressure. The temperature at which the distillation is started is usually an azeotropic point of 1,2-dichloroethane-an C_{2-4} alcohol-water. For example, the azeotropic point of 1,2-dichloroethane-ethanol-water is 66.7°C, and the azeotropic point of 1,2-dichloroethane-isopropanol-water is 69.7°C, but these azeotropic points may vary under the influences of barometric pressure when the distillation is carried out or of molar elevation of boiling point, etc. The temperature at which the distillation is stopped may vary according to the kinds of

the aqueous C_{2-4} alcohol to be used, and it is usually in the range of from 78°C to 100°C, preferably in the range of from 85°C to 100°C, and more preferably in the range of 90°C to 100°C.

Page 10, please replace the paragraph spanning lines 6-14, with the following rewritten paragraph:

The starting crystals of zonisamide to be used in the present process may be prepared according to the method disclosed in Reference Example 3 and Example 1 of JP-A-53-77057, except for the solvent in Example 1. That is, it is prepared by reacting 1,2-benzisoxazole-3-methanesulfonyl chloride with ammonia in 1,2-dichloroethane as a solvent, concentrating the reaction mixture, adding water to the resulting residue, followed by collecting the precipitated crystals to give wet crystals containing zonisamide in an amount of about 85 % by weight.

Page 10, please replace the paragraph spanning line 24 through page 11, line 3, with the following rewritten paragraph:

The present invention is illustrated in more detail by the following Examples, but the present invention should not be construed to be limited thereto. The content of 1,2-dichloroethane ~~residing~~ in crystals of zonisamide was measured by gas chromatography.

Page 13, please replace the paragraph spanning line 18 through page 14, line 7, with the following rewritten paragraph:

INDUSTRIAL APPLICABILITY

By conventional methods for recrystallization, crystals of zonisamide containing residual 1,2-dichloroethane of not more than 5 ppm could not be obtained from the starting crystals of zonisamide prepared using 1,2-dichloroethane. On the contrary, the content of the residual 1,2-dichloroethane in the crystals of zonisamide prepared by the Examples of the present process is less than 1 ppm (less than detection limit), which is far lower than required 5 ppm. As shown in Example 4, the present process is effective and applicable even if there is a large residual amount of

1,2-dichloroethane ~~resides~~ in the starting crystals of zonisamide. In addition, as shown in Example 5, the yield of crystals of zonisamide is not so reduced even by subjecting them to the present process.